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Challenges in the treatment of elderly patients with primary central nervous system lymphoma

Roth, P ; Hoang-Xuan, K

Abstract: PURPOSE OF REVIEW: Approximately 50% of all patients with primary central nervous system lymphoma (PCNSL) are 60 years or older and may therefore be considered as elderly. Although the diagnostic work-up is basically the same in young and in elderly patients, therapeutic strategies vary considerably. Here, we review the characteristics of elderly PCNSL patients with a particular focus on advances in the optimization of treatment regimens. **RECENT FINDINGS:** Age has been repeatedly confirmed as a major therapy-independent negative prognostic factor. Benefit from treatment and the tolerability of tumor-specific therapy, particularly whole-brain radiotherapy, are significantly lower in the elderly patients. Still, for patients with newly diagnosed PCNSL, several studies emphasized the indisputable role of high-dose methotrexate as backbone for any therapy regimen also in elderly patients. However, the durability of responses to primary chemotherapy is significantly shorter than in young patients. Recent data from a randomized phase II study for elderly PCNSL patients suggest that the combination of high-dose methotrexate, procarbazine, vincristine and cytarabine is superior to methotrexate in combination with temozolomide. **SUMMARY:** Current efforts aim at treating elderly PCNSL patients within clinical trials that are specifically designed for this group of patients. Determining adapted consolidation and/or maintenance treatment to improve disease control in responding patients are the main challenges to be faced by future trials. Together with a better understanding of age-specific changes in the biology of PCNSL, this will pave the road for elderly tailored therapies.

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Challenges in the treatment of elderly patients with primary central nervous system lymphoma

Patrick Roth^a and Khê Hoang-Xuan^{b,c,d,e,f}

Purpose of review

Approximately 50% of all patients with primary central nervous system lymphoma (PCNSL) are 60 years or older and may therefore be considered as elderly. Although the diagnostic work-up is basically the same in young and in elderly patients, therapeutic strategies vary considerably. Here, we review the characteristics of elderly PCNSL patients with a particular focus on advances in the optimization of treatment regimens.

Recent findings

Age has been repeatedly confirmed as a major therapy-independent negative prognostic factor. Benefit from treatment and the tolerability of tumor-specific therapy, particularly whole-brain radiotherapy, are significantly lower in the elderly patients. Still, for patients with newly diagnosed PCNSL, several studies emphasized the indisputable role of high-dose methotrexate as backbone for any therapy regimen also in elderly patients. However, the durability of responses to primary chemotherapy is significantly shorter than in young patients. Recent data from a randomized phase II study for elderly PCNSL patients suggest that the combination of high-dose methotrexate, procarbazine, vincristine and cytarabine is superior to methotrexate in combination with temozolomide.

Summary

Current efforts aim at treating elderly PCNSL patients within clinical trials that are specifically designed for this group of patients. Determining adapted consolidation and/or maintenance treatment to improve disease control in responding patients are the main challenges to be faced by future trials. Together with a better understanding of age-specific changes in the biology of PCNSL, this will pave the road for elderly tailored therapies.

Keywords

age, elderly, primary central nervous system lymphoma, treatment

INTRODUCTION

Although a rather rare disease, primary central nervous system lymphoma (PCNSL) has always been a neoplasm of particular interest since it is potentially curable, which is in sharp contrast to most other malignant brain tumors. Approximately 50% of all PCNSL patients are 60 years or older, and the proportion of elderly patients diagnosed with PCNSL is increasing for unknown reasons [1]. In the elderly population, however, cure is much less frequently achieved [2]. It has long been recognized that age at diagnosis is one of the strongest negative prognostic factors in PCNSL. Most likely, it is not higher age *per se*, but rather the presence of various comorbidities in the elderly patients that make them more susceptible to treatment-related side-effects. Furthermore, elderly patients are more likely to be on other medications with a potential of pharmacological interactions that can translate into either reduced activity of the tumor-specific

treatment or unwanted side-effects [3]. However, it cannot be excluded that the negative prognostic value of age partially reflects age-specific alterations in the biology of these tumors that contribute to therapy resistance.

Owing to its strong prognostic impact, all scores aiming at classifying patients into prognostic subgroups encompass age as an important parameter. Overall, the term ‘elderly’ remains poorly defined,

^aDepartment of Neurology and Brain Tumor Center, University Hospital Zurich, Zurich, Switzerland, ^bAPHP, Department of Neurology, Groupe Hospitalier Pitié-Salpêtrière, ^cSorbonne Universités, UPMC Univ Paris 06, UM 75, ^dICM, ^eLOC Network and ^fIHU Paris, France

Correspondence to Dr Patrick Roth, MD, Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland. Tel: +41 44 255 5511; fax: +41 44 255 4380; e-mail: patrick.roth@usz.ch

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KEY POINTS

- Age is an important treatment-independent prognostic factor in PCNSL patients.
- Elderly patients are at increased risk of suffering from severe side-effects from WBRT and chemotherapy.
- HD-MTX should be administered to elderly patients whenever possible since convincing alternatives are lacking.
- The combination of HD-MTX and WBRT results in the development of dementia in the majority of elderly patients and must therefore be avoided.
- Future trials for elderly PCNSL patients must aim at defining more active regimens with good tolerability in order to preserve quality of life and autonomy.

and there is no consensus on the optimal cut-off, which is typically made at age 60 or 65 years. However, particularly between 60 and 70 years, there are considerable interindividual differences in the overall constitution that preclude a definitive cut-off for separation between 'young' and 'elderly'. Although the 'Memorial Sloan-Kettering Cancer Center prognostic model' uses a cut-off even at age 50 years, the IELSG score divides patients with a cut-off at age 60 years [4,5]. Whether the importance of age can be depicted by a single cut-off or whether at least three age categories may allow for a more appropriate patient stratification has not yet been defined. Treatment decisions in patients aging from 60 to 70 years should therefore be guided not only by age but by additional criteria summarized by the term 'frailty', which involves the overall performance status as well as comorbidities and thus indicates an increased risk of intolerance of more intense therapy.

In general, elderly cancer patients are more likely to develop cognitive impairment as a result of tumor-specific therapy [6]. The risk is even higher in patients suffering from PCNSL owing to the fact that the tumor resides in the brain, which is therefore a direct target of local therapies such as whole-brain radiation therapy (WBRT). Not surprisingly, severe neurotoxicity is frequent in elderly PCNSL patients treated with WBRT [7]. Similarly, combinatorial approaches including WBRT led to profound cognitive impairment [8–10]. However, not only WBRT but also systemic therapies increase the risk for the development of cognitive decline. This phenomenon, also known as '*chemobrain*', is more common in the elderly patients [11]. Furthermore, intense treatment regimens such as high-dose chemotherapy with subsequent autologous stem

cell transplantation are restricted to the younger patient population because of their systemic toxicity. Accordingly, treatment of PCNSL in the elderly patients strives for the maintenance of quality of life and preservation of functional independence with a particular focus on neurocognitive function rather than for cure.

Age-related molecular genetic characteristics in PCNSL tumor tissue have not been identified so far. Hence, an age-dependent frequency and prognostic role of specific gene mutations such as isocitrate dehydrogenase gene mutations in gliomas has not yet been described in PCNSL [12,13[¶]]. It needs to be awaited whether such molecular markers, which may account for the negative prognostic impact of age, will become available in the future. However, detailed molecular analyses of PCNSL specimens are commonly limited by the available amount of tissue, typically obtained by a biopsy-only approach. Still, it might be possible that comprehensive analyses of PCNSL samples will be accomplished within the next years. Similar to other brain tumors, such high-throughput-profiling approaches may allow for the detection of age-specific alterations that could then be exploited for treatment stratification.

TREATMENT: GENERAL CONSIDERATIONS

Histopathological confirmation of a CNS lymphoma must be followed by a staging evaluation. The diagnostic procedures, which primarily aim at excluding the presence of concomitant systemic lymphoma, do not differ between young and elderly patients [14]. Upon completion, treatment should start as soon as possible to avoid further tumor growth and clinical deterioration.

The role of surgery has been limited for decades to bioptic sampling of tumor tissue, which is sufficient for a histopathological diagnosis. However, a more recent analysis suggests that complete or partial resection of PCNSL translates into prolonged progression-free survival (PFS) and overall survival (OS), at least in patients with single brain lesions [15]. Accordingly, also in the elderly patients, tumor resection should be considered when a lymphoma is suspected and surgery can be carried out with a manageable risk of postoperative deficits and perioperative morbidity. Obviously, this situation will be mainly found in patients who present without severe comorbidities with a single and rather superficially located tumor mass.

Although WBRT may result in high response rates, it typically does not confer long-lasting remissions [16]. Furthermore, because of its deleterious effects on the neurocognitive function, it has been

Table 1. Prospective trials using high-dose methotrexate-based therapy in elderly patients

	n	Median age (years)	Treatment	CR	PR	PFS	OS
Omuro <i>et al.</i> [28]	23	68	MTX, temozolomide	55%	0%	8	35
Hoang-Xuan <i>et al.</i> [29]	50	72	MTX, CCNU, procarbazine, prednisolone MTX and cytarabine intrathecal	42%	6%	10.6	14.3
Illerhaus <i>et al.</i> [30]	30	70	MTX, CCNU, procarbazine	44%	26%	5.9	15.4
Fritsch <i>et al.</i> [31]	28	76	MTX, CCNU, procarbazine, rituximab	64%	18%	16	17.5
Roth <i>et al.</i> [19]	126	73	MTX, ifosfamide, +/-WBRT	30%	14%	4.0	12.5
Omuro <i>et al.</i> [32 ^{***}]	95	73	MTX, procarbazine, vincristine, cytarabine MTX, temozolomide	62% 45%	26% 20%	9.5 6.1	31 14

CR, complete response; MTX, methotrexate; OS, overall survival; PFS, progression-free survival; PR, partial response; WBRT, whole-brain radiation therapy.

largely abandoned in elderly patients as first-line treatment. In contrast, high-dose methotrexate (HD-MTX) has become the backbone of any treatment regimen for PCNSL, also in elderly patients. The combination of HD-MTX with other chemotherapeutic drugs has resulted in increased response rates in young and elderly patients. However, a proof of superiority of these combinatorial approaches in terms of prolonging OS is lacking [17]. In contrast, it became clear that elderly PCNSL patients are more likely to experience relevant side-effects from polychemotherapy. As in young patients, consolidating WBRT does not prolong OS but is associated with increased toxicity in elderly patients [18,19]. Therefore, it remains to be determined which drug(s) should be added to HD-MTX. There is no standard of care for elderly patients who are definitively ineligible for HD-MTX-based therapy. Treatment with the alkylating agent temozolomide (TMZ) alone resulted in low response rates and overall poor survival in elderly patients [20]. Here, WBRT may be used as a rescue strategy despite its drawbacks mentioned above.

CLINICAL TRIALS FOR ELDERLY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA PATIENTS

Elderly patients are frequently underrepresented in clinical trials [21] because such trials had upper age limits or elderly patients did not comply with inclusion criteria, for example, because of comorbidities. In contrast to young patients in whom the diagnosis of PCNSL is typically the only severe diagnosis, elderly patients are much more likely to suffer from one or more additional comorbidities that preclude intense therapy regimens [22]. Still, the successful completion of elderly trials in PCNSL demonstrates that such studies are feasible and

enrolment of patients into open trials should be encouraged whenever possible.

HD-MTX doses of at least 3 g/m² result in sufficient CNS levels that are cytotoxic to lymphoma cells [8]. Treatment with HD-MTX can be associated with significant toxicity, and some physicians are hesitant to use it in elderly patients. However, retrospective series of patients treated with HD-MTX monotherapy alone indicate that it is active and can be administered safely to elderly patients [23,24]. The high response rates reported here may result from patient selection as well as the retrospective nature of these series and could not be reproduced in prospective trials (see below). Reductions of the MTX dose are required more frequently in the elderly patients and should be done on the basis of the glomerular filtration rate before each treatment cycle. Termination of MTX treatment because of MTX-related toxicity or delayed serum MTX clearance was observed to a similar extent in young and elderly patients when the MTX dose was calculated in a glomerular filtration rate-dependent manner [25]. Exceedingly, high MTX area under the curve levels may reduce PFS and OS in elderly patients and should therefore be avoided [26]. Nevertheless, a series of patients aged 80 years or higher demonstrated that the administration of HD-MTX is feasible even in the oldest patients [27].

Similar to young patients, treatment with HD-MTX alone was considered not active enough and several prospective trials, specifically designed for the elderly patients, aimed at assessing the efficacy of HD-MTX in combination with various other compounds (Table 1) [18,28–31,32^{***}]. The EORTC conducted the first multicenter phase II trial devoted to the elderly patients, which evaluated a combination including HD-MTX (1 g/m²), CCNU, procarbazine and MTX/cytarabine intrathecal

chemotherapy without WBRT as initial treatment. A 42% complete response (CR) rate as well as a median PFS and OS of 10 months and 14.3 months, respectively, were reported with an acceptable tolerance and good preservation of cognitive function in long-term survivors [29]. Illerhaus *et al.* [30] evaluated a modified MTX/CCNU/procarbazine regimen using a higher dose of MTX (3 g/m^2), allowing cytotoxic MTX levels in the CSF and avoiding intrathecal therapy. Similar results, compared with the EORTC regimen, were obtained in terms of CR rate and OS. Subsequently, the same group added rituximab to their regimen and reported a higher CR rate (64%) and longer PFS (median of 16 months), but these numbers did not translate into an improved OS [31]. Altogether, the combination of HD-MTX, CCNU and procarbazine (with or without rituximab) appears to be an active and relatively well tolerated regimen, considering the premorbid characteristics of the elderly population. Another combination consisting of HD-MTX (3 g/m^2) and TMZ ($150\text{--}200 \text{ mg/m}^2$) has been evaluated and reported comparable results to those of the EORTC regimen in terms of CR rate and PFS, except the longer OS observed, which is most probably explained by a high rate of patients receiving salvage treatment at relapse [28]. Formal comparisons of different chemotherapy regimens have not been published. However, in a recently completed ANOCEF randomized phase II study that evaluated two HD-MTX-based polychemotherapy regimens, that is, MPV-A (HD-MTX, procarbazine, vincristine, cytarabine) and M-T (HD-MTX, TMZ), the toxicity was identical and all efficacy criteria (CR, PFS, OS) appeared better with MPV-A than with M-T, although the differences were not significant [32^{***}].

The G-PCNSL-SG-1 trial is the only completed phase III study in PCNSL. The results of this trial indicated that WBRT following HD-MTX-based chemotherapy has no impact on OS. The study was not specifically designed for elderly patients. However, 126 out of 526 eligible patients were 70 years or older, allowing for a detailed analysis of the characteristics of the elderly population. The overall response rate upon HD-MTX-based chemotherapy was significantly lower in the elderly patients. Furthermore, there was a higher rate of grade III/IV leukopenia in the elderly patients, whereas acute toxicity was otherwise age-independent. PFS (4.0 versus 7.7 months) and OS (12.5 versus 26.2 months) were significantly shorter, and tumor recurrence after CR occurred dramatically earlier in elderly patients compared with the group of young patients (16.1 versus 35.0 months) [19]. The latter indicates that elderly CR patients require

consolidation and/or maintenance approaches that will need to be defined in the future. A randomized phase III trial comparing maintenance chemotherapy versus observation in this setting is currently planned in France. Reduced dose WBRT has been proposed as consolidation with a lowered risk of neurotoxicity [33]. However, only few elderly patients had a neuropsychological follow-up in this study (only three out of 12 evaluated patients were older than 60 years), and the benefit both in terms of efficacy and neurotoxicity, particularly in this population, is questionable [19,34]. The CALGB50202 multicenter phase II trial reported promising results using high-dose cytarabine combined with etoposide as consolidation following a HD-MTX-based induction regimen. Of note, patients aged 60 years or older did as well as younger patients [35^{***}].

Regardless of age, no standard of care exists for patients with recurrent PCNSL. Randomized trials are lacking and the choice of therapy depends on various parameters such as the response to first-line treatment, time elapsed from last treatment, performance status and residual side-effects from previous therapies. Similar to the situation with newly diagnosed disease, higher age requires specific considerations with regard to comorbidities, side-effects and interactions with other drugs. An analysis of patients treated within the G-PCNSL-SG1 trial indicates that elderly patients are treated less frequently and less aggressively at recurrence [19]. Rechallenge with HD-MTX-based regimens, radiation therapy – despite its unfavorable toxicity profile in elderly patients – and various chemotherapy agents such as TMZ are among the available options that have been summarized elsewhere [36,37].

CONCLUSION

Elderly patients represent an important population of all PCNSL patients. Age has repeatedly shown to be a negative prognostic factor, and the intense treatment regimens administered to young patients aiming at a cure are not suitable for the elderly patients. Until now, only few trials dedicated to the specific needs of elderly PCNSL patients have been performed. Whenever possible, HD-MTX remains the backbone of any successful therapy in the elderly patients. However, similar to young patients, the value of combinatorial approaches with other drugs must be determined within clinical trials. The design of these studies must respect the specific needs of elderly patients, including their increased risk of suffering from significant side-effects. Treating as many patients as possible within such trials must be pursued to allow for optimized treatment regimens.

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Conflicts of interest

P.R. has received honoraria for advisory boards from Roche, MSD and Molecular Partners. K.H.-X. has no conflict of interest.

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